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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,589	06/08/2000	Katherine A. High	CHOP-0019 / CHOP-0088U	1864

23377 7590 02/26/2008
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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
02/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,24,28 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,24,28 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/11/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/11/2007 has been entered.

Applicant's response and amendment to the claims filed June 11, 2007 has been received and entered. Claims 3-23, 25-27, 29-42 have been canceled, while claims 1, 24, 28 have been amended. Applicants have also added claim 43 generally directed to elected invention. Claims 1-2, 24, 28 and 43 are pending in the instant application.

Rejections set forth in this office action are the only rejections pending in the instant application. Any rejection not repeated in this office action has been withdrawn.

New Grounds of Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 24, 28 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

It is noted that although instant claims are directed to a method of preventing the formation of inhibitory antibodies to Factor IX delivered to a mammal by way of an adeno-associated viral (AAV) vector, they have been analyzed for their intended effect on correcting hemophilia B in any mammal including humans by delivering to any site and any dose of AAV comprising factor IX.

The aspects considered broad are the breadth of subject population, using any dose and serotype of AAV that could be delivered for the treatment of hemophilia B and prevention of formation of inhibitory antibodies to Factor IX, any site of administration to affect genetic defect caused by the lack of Factor IX and transgene not operably linked to expression control elements a critical limitation not described in claims. As stated before although claims are directed to method of preventing the formation of antibodies by administering cyclophosphamide prior or simultaneously with AAV comprising gene encoding Factor IX, therefore, the nature of such invention is within the broad genera of gene therapy, and gene therapy is not generally enabling due to problems with, *inter alia*, targeting and expression of transgenes at therapeutically effective level by administering composition via any route and method in a target tissue. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification broadly discloses the need for improved methods of delivering FIX to mammals, in particular, to humans, having hemophilia such that a therapeutic effect could be achieved (se page 4, lines 1-2). The invention is based in part on administering to the mammal an immunosuppressive agent in conjunction with the gene therapy (see page 4, lines 9-11). Pages 5 and 6 provide brief description of the drawing and definition of the claimed embodiments. It is noted that prior to instant invention, Kay et al. (1997, Proc. Natl. Acad. Sci. USA 94:4586-4691, IDS) have described the use of immunomodulatory agents to block the immune response to a gene therapy vector; however, this disclosure of Kay et al does not teach the use of immuno- suppressive agents for the purpose of inhibiting antibody development directed against the gene encoding a therapeutic protein. In the instant case, specification contemplates directing inhibition of the generation of antibody specific for the therapeutic gene product. It is noted that guidance provided in the specification is limited to the multiple administration of cyclophosphamide via specific route in conjunction with delivering to a specific site,

a specific dose of AAV containing gene encoding Factor IX and as such instant broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that FIX can be expressed in any cells of humans at minimum effective levels required for therapeutic response. The specification does not provide any specific guidance for preventing the formation of inhibitory antibodies to Factor IX in a predictable animal model that could be correlated to the breadth of the claims intended to treat hemophilia.

The guidance provided in the specification clearly indicates that the only intended use for this invention is for human gene therapy; however, this intended use is not enabled. This is particularly important since prior to instant invention, the state of the art effectively summarized by the references of Kaiser (Science, 317, 2007, 580) and Chao et al (The Mount Sinai J of Medicine, 2004, 305-312) describes progress and failures in achieving desired effects after human gene therapy (see Chao et al page 310, col. 2, para. 1 and Kaiser et al, para 580, col. 3, para. 2), suggesting vector targeting *in vivo* to be unpredictable and inefficient. In fact, gene delivery and gene therapy at the time of the filing of this application was unpredictable as numerous factors complicated the gene delivery art that is difficult to be overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (Ecke, Goodman & Gilman's The Pharmacological basis of Therapeutics, 1996, McGraw-Hill, New York, NY. pp 77-101). These observations are further supported by Walsh (Gene Therapy, 2003, 10, 999-1003) who while reviewing the state of gene

therapy in hemophilias states "AAV2 vectors carrying human factor IX cassettes delivered via the hepatic artery resulted in lower level of expression" (see page 1001, col. 2, para. 2). Walsh concludes that a review of the preclinical data suggests that animal studies may not be predictive of the outcome in humans. Walsh specifically discloses that vector dosing based on a vector particle-to-weight ratio produced discrepant results when comparing equivalent AAV vector dosing in mice and hemophilic dogs. Whereas experiments in hemophilic mice are dose-dependent and can produce supraphysiologic levels of factor IX (300% of normal), equivalent doses in hemophilic dogs produce factor IX at levels around 5% of normal and do not appear to be dose-dependent. Recent data testing AAV2/human factor IX vectors in non-human primates produced 4–10% factor IX, similar to data generated in hemophilic dogs for a period of 1 year. Walsh asserts that these preclinical outcomes reflect that species differences in terms of rate of infectivity, gene expression, protein modification and processing (see page 1001, col. 2, last para.). The specification does not provide nexus between the data obtained in rodent and canine model to similar effect in humans. Given the unpredictability in the animal studies (see Walsh, above), one of skill in the art could not rely upon the art to predictably achieve hemophilia gene therapy in humans. Additionally, given differences in the outcome of expression level in different species, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to establish the levels of the transgene expression, the consequences of that expression, and therefore, the resulting treatment of hemophilia in humans, as embraced by the breadth of the claims.

Applicant's examples describe intramuscularly injecting hemophilia knockout mice with an adeno-associated virus (AAV) vector encoding the murine FIX transgene (1 X 10^{11} vector genomes/mouse) with or without immuno modulation therapy. The aPTT and Bethesda titer assay showed the evidence of inhibitory activity in mice (see figure 2 and 3). The data shows that cyclophosphamide treated

mice did not develop antibodies through the five months of observation (see figure 3 and 4). The art of record only teaches the potential benefit of administering cyclophosphamide prior or simultaneously with gene therapy vector for preventing antibody formation to FIX , however, such specification fails to correlates the data obtained in rodent model to any other model that could be extrapolated to the breadth of the claims. It is not enough to reasonably predict that the gene encoding FIX can be expressed using any serotype of AAV vectors delivered via any route to any site at reasonable level for appropriate time duration in appropriate tissue for the intended correction of hemophilic condition. It is also not apparent how the claimed vectors or other delivery vehicle would be effective in any mammal. Artisan could not predict, in the absence of proof to the contrary, that such a method would be efficacious in any prophylactic or therapeutic method. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (1) how an artisan of skill would have practiced the claimed method in any mammal (ii) the claimed method would have resulted in expression of factor IX in amount sufficient to have the intended biological effect in treating the hemophilic conditions in "any mammal". See also, the above cited art of Walsh, which clearly teaches the unpredictability between species (rodent and canine), with respect to hemophilia gene therapy. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of gene therapy and gene delivery *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

The state of the art summarized by the post filing reference of Arruda et al (Blood, 2004, 103(1) 85-92) shows that transient immuno suppression with cyclophosphamide could prevent inhibitor formation in dogs treated at higher doses and in nonsense mutation dogs. Arruda discloses that the combination of dose reduction and transient immunosuppression by cyclophosphamide initially

appeared successful, as there was no evidence of inhibitory antibody formation however, three weeks after cyclophosphamide therapy the animal developed a bleed in the hindlimb and was subsequently treated with canine plasma. After the plasma transfusion, an inhibitor was detected (see page 89, col.2, and last para.). It is noted that applicants' own work after several years after filing of this application list some of the factors that influence the risk of inhibitor formation in the setting of gene transfer including "[u]nderlying mutation, the vector itself, the route of administration, the presence or absence of a tissue-specific promoter, and the dose" Arruda states, [a] complex interplay among these factors may control the eventual outcome, so that, for example, an innate immune response to a virally derived vector may promote an adaptive immune response to the transgene product" (See page 91, col. 1, last para. to col. 2, para. 1). Additionally, Arruda et al (Blood. 2005 May 1;105(9):3458-64) in an other post filing art teaches that peripheral intravenous delivery of rAAV to a hemophilia B dog results in sub therapeutic FIX levels (See page 3641, col. 2, para. 3). In the instant case, the guidance provided in the specification is limited to intramuscular injection of AAVmFIX ($1x10^{11}$) with or without immunotherapy. The teaching of Arruda et al (Blood. 2005) clearly shows that gene delivery method in hemophilia is critical to the resulting outcome in patient. The specification fails to provide nexus between direct injection of vector to different delivery method described in Arruda. Additionally, although Arruda et al used $1.7\text{-}3x10^{12}$ vg/kg to compare the several different gene delivery method including intravascular, peripheral to study the transduction of FIX, but given that the outcome of expression level in different species, particularly when taken with the lack of guidance in the specification with respect to intravascular gene delivery method, it is reasonable to state that one of ordinary skill in the art would have to perform undue experimentation to determine appropriate serotype and gene delivery method of AAV in the treatment of hemophilia B.

Claims are directed to a method of preventing the formation of inhibitory antibodies to Factor IX by intravenously or intraperitoneally administering to mammal cyclophosphamide prior or simultaneously with AAV vector comprising Factor IX before formation of antibodies, wherein factor IX is from the same species of mammal. Subsequent claim limit the method of claim 1 to include mammal and gene that are human. The guidance provided in the specification is limited intra muscular injection of an AAV vector encoding the murine FIX transgene (1×10^{11} vector genomes/mouse) with or without immuno modulation therapy to a hemophilia knockout mouse. The specification fails to correlates the data in mouse model to the breadth of the claims embracing delivering to any site, any serotype, and dose of AAV containing gene encoding Factor IX. Prior and post filing art teaches that gene therapy approaches that are effective in inbred mice often fail in humans. Ponder et al (Current Opinion Hematol, 2006, 13, 301-307) describe the to difficulties in scaling up to larger animals, or to the biology of animals with a longer life span (see page 303, col. 1, last para bridging to col. 2). The specification also does not provide any guidance as to how studies in rodent models could be extrapolated to human situations for the treatment of hemophilia as recited in the instant invention Additionally, pseudotyped vectors with capsid proteins from other AAV serotypes are more efficient at transducing liver in mice than are AAV2 vectors. Ponder cites other references to indicate that neither AAV6 nor AAV8 vectors are more effective than AAV2 at expressing canine FVIII in dogs with hemophilia A in one study, however, in an other study, expression of canine FIX from an AAV8 vector was 2-fold that from an AAV2 vector in dogs with hemophilia B, while expression from AAV5 was lower than that from AAV2 (see page 303, entire col. 2). These studies clearly indicate that different capsid protein from AAV serotype have different expression pattern and subject to variable biological effect. The specification does not provide adequate guidance with respect to type of AAV serotype that would show intended therapeutic effect in the claimed embodiments.

In a recent post filing report, Manno et al (Nature Medicine, 2006, 12(3), 342-347) describe infusing rAAV-2 vector through the hepatic artery into seven subjects for expression of human FIX. It is noted that this gene delivery resulted in to asymptomatic elevation of liver transaminases and cell-mediated immunity targeting antigens of the AAV capsid causing both the decline in FIX and the transient transaminitis (see abstract). Manno hypothesizes several possibilities for transaminitis including specific destruction of vector-transduced cells by the immune system and AAV capsid being targeted by the immune cells (see page 346, col. 1, para. 1). Therefore, methods of prevention of the formation of inhibitory antibodies to Factor IX in a mouse model using specific dose and serotype of AAV delivered by specific route cannot be directly extrapolated to prevention of the formation of inhibitory antibodies to Factor IX in any other mammal. The specification also does not provide any guidance as to how studies directed to intramuscular injection of AAV 1 X 10^{11} vector genomes/mouse) with or without immuno modulation therapy can be extrapolated to the treatment of hemophilia in humans. This is particularly important since it is generally known that vector delivery play in the scale-up from mouse to dog to human. Arruda et al (Blood. 2005;105(9):3458-64) reported that a dose of 1 x 10^{13} vg/kg yielded circulating FIX levels of 5% to 7% in the mice, and only 1% to 2% in hemophilic dogs. This decline in efficacy with increasing size was not entirely clear even after five years of filing of this application. Arruda speculate that interspecies differences in promoter activity (ie, a cause not related to size), or diffusion distance of the product to the circulation (more clearly related to size of organism) might account for the difference (see page 3463, col. 1, para. 3). Furthermore, it is also noted that, the specification does not teach which serotype, dose, route or site AAV that could be effective in administering transgene in any mammal including humans. In addition, prior art at the time of filing of this application as described before did not provide any convincing guidance in this regard either. It is noted that the unpredictability of a

particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).* It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994),* citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).* Given the breadth of the claims and the guidance provided by the specification it would have required undue experimentation to make and use the method of preventing the formation of inhibitory antibodies to Factor IX intended for the treatment of hemophilia B in a human, by one of skill in the art without a reasonable expectation of success.

The scope of invention as claimed encompasses a method of preventing the formation of inhibitory antibodies to Factor IX by administering to mammal cyclophosphamide prior or simultaneously with AAV vector containing gene encoding FIX via any route of administration (i.e oral, intranasal, intramuscular, intravenous, subcutaneous etc.). It has been difficult to predict the efficacy and outcome of transduced therapeutic gene because several factors govern the expression and/or therapeutic potential of transduced gene *in vivo.* The transduction of target cells represents the first critical step in any gene based therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. In addition, besides the limitations in gene transfer the problem to selectively target cells *in vivo* is still one of the most difficult obstacles to overcome (as discussed before, supra). For example, upon systemic administration the viral and non-viral particle may bind to many cells they encounter in vivo and therefore would be diluted before reaching their targets. Besides direct administration into rat myocardium, the specification merely contemplates plurality of route without providing any specifics or showing that other routes of administration would result in expression in target cells For instance, Gautam et al (Am J Respir Med, 2002;1(1):35-46; abstract) discloses the

use of different vector delivery routes to the lung, such as intravenous injection, intratracheal installation, and aerosol with varying degrees of success. In fact, Xiao (Mol Ther. 2000; 1(4):323-9, IDS) emphasized that the route of vector administration has a qualitative effect on anti vector B cell responses. Xiao exemplified that administration of vector into the tail vein resulted in T-cell-dependent (TD) B cell responses which was completely inhibited with depleting CD4 antibody, while delivery of vector into the portal circulation via the spleen resulted in B cell response that was partially T cell independent (TI) rendering strategies based on T cell inhibition ineffective in allowing vector re-administration; It is noted that even after filing of this application Xiao et al disclose that the precise contributions of TI and TD responses to neutralizing antibodies induced following intraportal administration of AAV in nonhuman primates was not clearly established. Xiao et al emphasizes the need for more studies with immune-suppressive strategies to inhibit T cell responses is required to dissect the TI and TD components of the AAV– neutralizing antibodies responses in nonhuman primates and potentially humans (See page 328, col. 1, para. 2).The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in any mammal including human by administering cyclophosphamide with any dose of AAV to any site via any route resulting in inhibition of antibody to vector encoding therapeutic gene. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of the gene delivery was not routine rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

In conclusion, in view of breadth of the claims and absence of adequate showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not

enabled for the claimed inventions. The specification and prior art do not teach a method of preventing the formation of antibodies by administering cyclophosphamide prior or simultaneously with AAV comprising gene encoding Factor IX. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of gene delivery intended for gene therapy, with the intended use for humans, with any AAV comprising gene encoding FIX was unpredictable at the time of filing of this application as supported by the observations in the art record.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Smith et al (Gene Therapy (1996), 3(6), 496-502) and Dwarki et al (WO9906562).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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